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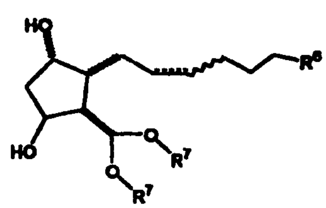
(54) Title: A PROCESS FOR MAKING PROSTAGLANDIN F ANALOGS



(A)

(57) Abstract

Described is a process for making prostaglandin F analogs, the process comprising the steps of: I) preparing an intermediate having a structure according to Formula (A): wherein R^6 and R^7 are as defined in the specification; wherein the preparation comprises: (a) reacting a Corey aldehyde with an activated alcohol to form an acetal derivative; (b) deprotecting the acetal derivative of step (a) to form a hydroxy acetal; (c) optionally reprotecting the hydroxy acetal of step (b); (d) reducing (b) or (c) to provide a lactol derivative; and (e) condensing the lactol derivative of step (d) with a phosphonium salt to form the intermediate ketal of Formula (A), or a salt or protected form thereof; II) removing the ketal form the intermediate of Formula (A) formed in step (I) to form an aldehyde and coupling the aldehyde with a Wadsworth-Horner-Emmons reagent or a Wittig-Horner reagent to form a product, and III) conducting one or more subsequent synthetic steps on the product of step (II) to form a prostaglandin F analog.

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A PROCESS FOR MAKING PROSTAGLANDIN F ANALOGS

CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/058,253, filed September 9, 1997.

FIELD OF INVENTION

The present invention describes a process for making prostaglandin F analogs, including 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F1_{\alpha}$ analogs.

BACKGROUND OF INVENTION

The present invention describes a process for making prostaglandin F analogs, especially 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F1_{\alpha}$ analogs. Such derivatives are useful for the treatment of many medical disorders including, for example, ocular disorder, hypertension, fertility control, and osteoporosis. The prostaglandin 13,14-dihydro $PGF1_{\alpha}$, disclosed in U.S. Patent No. 3,776,938 (1973) by S. Bergstrom, et al. has a stimulatory effect on smooth muscle contraction as shown by test strips of guinea pig ileum, rabbit duodenum, or gerbil colon.

Further information regarding the biological effects of 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F1_{\alpha}$ analogs are disclosed in the following references: U.S. Patent No. 3,882,241 issued May 6, 1975 to G. Pharriss; G.B. Patent No. 1,456,512 (1976) issued to Pfizer Inc.; Bundy, G. L.; Lincoln, F. H., "Synthesis of 17-Phenyl-18,19,20-trinor prostaglandins I. The PG1 Series", Prostaglandins Vol. 9 (1975) pp. 1-4.; CRC Handbook of Eicosanoids: Prostaglandins and Related Lipids Vol. 1, Chemical and Biochemical Aspects, Parts A & B, A. L. Willis, eds., CRC Press (1987); Liljebris, C.; et. al." Derivatives of 17-Phenyl-18,19,20-trinorprostaglandin $F_{2\alpha}$ Isopropyl Ester: Potential Antiglaucoma Agents", Journal of Medicinal Chemistry Vol. 38, (1995), pp. 289-304; Collins, P. W.; Djuric, S. W. "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chemical Reviews 93 (1993), pp. 1533-1564.

In the art, 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F1_{\alpha}$ analogs have been synthesized according to several different methods. See, G.B. Patent No. 1,040,544 issued to A. C. Chapman; G.B. Patent No. 1,186,505 issued to the Upjohn Co.; U.S. Pat nt No. 3,505,386 issued April 7, 1970 to J. Babcock et al.; U.S. Patent No. 3,435,053 issued

March 25, 1969 to Beal et al; G.B. Patent No. 1,251,750 issued to the Upjohn Co.; Bundy, G. L.; Lincoln, F. H. "Synthesis of 17-Phenyl-18,19,20-trinorprostaglandins I. The PG_1 Series" Prostaglandins, Vol. 9 (1975), pp. 1-4.

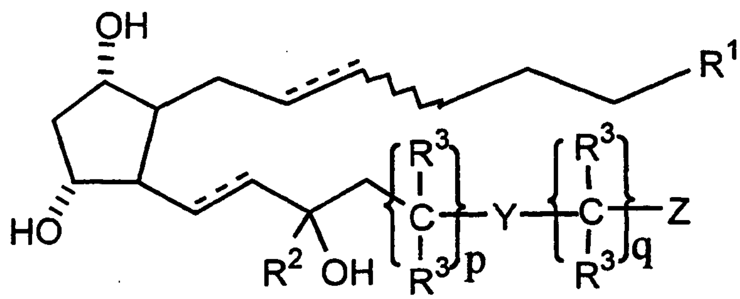
To date, the synthesis of 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F_{1\alpha}$ analogs has involved either conversion of the 13,14-dihydro prostaglandin E_1 skeleton (see Sjovall, et al., U.S. Patent No. 3,776,938) via reduction of the carbonyl moiety at C_9 (prostaglandin numbering) to the alcohol or by exhaustive hydrogenation of the preassembled $PGF_{2\alpha}$ skeleton (see, for example: Bundy, G. L.; Lincoln, F. H. " Synthesis of 17-Phenyl-18,19,20-trinorprostaglandins I. The PG_1 Series" Prostaglandins, Vol. 9 (1975), pp. 1-4.) The prostaglandin $F_{2\alpha}$ skeleton is prepared in a variety of ways, but generally from (i) the condensation of the Corey aldehyde [see, for example: Corey, E.J.; Weinshenker, N.M.; Schaaf, T.K.; Huber, W. " Stereo-Controlled Synthesis of Prostglandins $F_{2\alpha}$ and E_2 (*dl*)" J. Am. Chem. Soc. 1969, 91(20), p.5675-5677] with the appropriate oxophosphonate, followed by (ii) reduction at C_{15} (prostaglandin numbering) [see, for example: Noyori, R,; Tomino, I.; Yamada, M.; Nishizawa, M. " Synthetic Applications of the Enantioselective Reduction by Binaphthol-Modified Lithium Aluminum Hydride Reagents" J. Amer. Chem. Soc. 1984, 106, p. 6717-6725.], (iii) reduction to the lactol and (iv) addition of the C_1-C_7 (prostaglandin numbering) side-chain (see, for example: G.B. Patent No. 1,456,512). For other methods to prepare the prostaglandin $F_{2\alpha}$ skeleton for conversion into the 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F_{1\alpha}$ analogs, see Collins, P. W.; Djuric, S. W. "Synthesis of Therapeutically Useful Prostaglandin and Prostacyclin Analogs", Chemical Reviews, 93, (1993), pp. 1533-1564.

It is apparent from the prior art that a higher yielding, more economical method for preparing prostaglandin F analogs, particularly 13,14-dihydro-15, 16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F_{1\alpha}$, analogs would be advantageous. It has been surprisingly discovered that the disadvantages of the lengthy literature procedures to the 13, 14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F_{1\alpha}$ analogs cited previously can be overcome using a novel method of protecting the Corey aldehyde using an activated (e.g., *bis*-trimethylsilyl) diol (e.g., ethylene glycol) or two equivalents of an activated monohydric alcohol. This procedure allows for the convenient synthesis of an advanced intermediate, the diol-protected aldehyde with the top chain in place. This intermediate allows for the rapid synthesis of final products via: 1) a Wadsworth-Horner-Emmons coupling of the desired substrate without prior protection of the alcohols, or a similar olefination reaction; 2)

reduction of the unsaturated ketone with cerium salts and sodium borohydride; 3) removal, if desired, of the alkenes by hydrogenation over palladium on carbon. The intermediates in these steps may be, depending on the substitution pattern, valuable biological agents in their own right, and this process is also useful for their individual preparation. Furthermore, when the atom stereochemistry is not specified, it is recognized that each diastereomer individually, and/or mixtures in varying proportions, are contemplated by this invention. is recognized that the prostaglandin F analogs made according to the present process can be further reacted using well known chemistry to produce prostaglandin A and E analogs.

SUMMARY OF INVENTION

The present invention provides a process for making a prostaglandin F analog having a structure according to Formula (I):



(I)

wherein:

a) R^1 is CO_2H, C(O)NHOH, CO_2R^5, CH_2OH, $S(O)_2R^5$, $C(O)NHR^5$, $C(O)NHS(O)_2R^5$, or tetrazole; wherein R^5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;

b) R^2 is hydrogen or lower alkyl;

c) each R^3 is independently selected from the group consisting of hydrogen, lower alkyl, alkoxy, haloalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaraomatic ring;

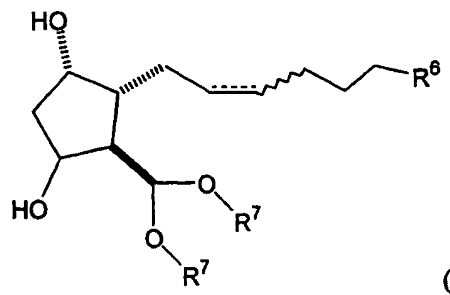
d) Y is NR^4, S, S(O), $S(O)_2$, O, or a bond, provided that no carbon has more than one heteroatom attached to it, wherein R^4 is hydrogen, lower alkyl, or acyl;

e) p is from 0 to 5, q is from 0 to 5, and p+q is from 0 to 5, provided that when Y is a bond p is at least 1; and

f) Z is hydrogen, methyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring, provided that when Y is S, S(O), or $S(O)_2$, Z is not hydrogen;

the process comprising the steps of:

I) preparing an intermediate having a structure according to Formula (A):



(A)

wherein (A) R^6 is a carboxylic acid, a carboxylic acid ester comprising a saturated or unsaturated, linear or branched C_1-C_8 alkyl, a carbocyclic ring, a hydroxamic acid, hydroxymethyl, sulfonic acid, sulfonyl ester, sulfonyl amide, or tetrazole; and (B)(i) each R^7 is lower alkyl, or (ii) the R^7 moieties together with the two oxygen atoms form a substituted or unsubstituted 5- or 6-membered monocyclic aliphatic heterocycle or a substituted or unsubstituted 8 to 12 member bicyclic aliphatic heterocycle; or a salt or protected form thereof.

wherein the preparation comprises:

(a) reacting a Corey aldehyde with an activated diol or two equivalents of an activated monohydric alcohol to form an acetal derivative;

(b) deprotecting the acetal derivative of step (a) to form a hydroxy acetal;

(c) optionally reprotecting the hydroxy acetal of step (b);

(d) reducing (b) or (c) to provide a lactol derivative; and

(e) condensing the lactol derivative of step (d) with a phosphonium salt to form the intermediate ketal of Formula (A), or a salt or protected form thereof;

II) removing the ketal from the intermediate of Formula (A) formed in step I) to form an aldehyde and coupling the aldehyde with a Wadsworth-Horner-Emmons reagent or a Wittig-Horner reagent to form a product, and

III) conducting one or more subsequent synthetic steps on the product of step II) to form a prostaglandin F analog of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes a process for the manufacture of prostaglandin F analogs. The process is particularly useful for preparing 13,14-dihydro-15,16 or 17-substituted-16-tetranor or 17-trinor prostaglandin $F_{1\alpha}$ analogs. Prostaglandin F derivatives are useful for

the treatment of many medical disorders including, for example, ocular disorders, hypertension, fertility control, nasal decongestion, and osteoporosis. When the compounds made according to this process are used for treating such disorders, they are to be in a pharmaceutically acceptable form. As used herein, such a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio. Such pharmaceutically acceptable forms include salts, biohydrolyzable esters and solvates.

The prostaglandin F analogs prepared according to the process of the present invention may be used as intermediates in the preparation of other prostaglandin analogs. That is, the compounds prepared may be reacted further, using known chemistry, to yield other active analogs, including prostaglandin A and E analogs.

I. Definitions and Usage of Terms

The following is a list of definitions and terms used herein:

"Activated diol" or "activated alcohol" is an alcohol which contains a silyl group rather than a hydrogen atom attached to the oxygen atom(s). A preferred silyl group on the activated diol/alcohol is trimethylsilyl.

"Alkyl" is a saturated or unsaturated hydrocarbon chain having 1 to about 18 carbon atoms, preferably 1 to about 12, more preferably 1 to about 6, more preferably still 1 to about 4 carbon atoms. "Lower alkyl" is an alkyl having from 1 to 4 carbon atoms. Alkyl chains may be straight or branched. Preferred branched alkyls have one or two branches, preferably one branch. Preferred alkyls are saturated. Unsaturated alkyls have one or more double bonds and/or one or more triple bonds. Preferred unsaturated alkyl have one or two double bonds or one triple bond, more preferably one double bond. Alkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred alkyls are unsubstituted. Preferred substituted alkyl are mono-, di-, or trisubstituted. Preferred alkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, and heteroaryl.

"Aromatic ring" is an aromatic hydrocarbon ring system. Aromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic aromatic rings contain from about 5 to about 10 carbon atoms, preferably from 5 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic aromatic rings contain from 8 to 12 carbon atoms, preferably 9 or 10 carbon atoms in the ring. Aromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred aromatic ring substituents include, for example, halo,

cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy, or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred aromatic rings include naphthyl and phenyl. The most preferred aromatic ring is phenyl.

"Base" means a basic reagent which is added to the reaction mixture to facilitate covalent bond formation in the Wadsworth-Horner-Emmons reaction. Bases include nitrogen bases. Preferred bases include those which are soluble in organic solvents and are volatile. Specifically, preferred bases include N, N diisopropylethylamine, triethylamine, trimethylamine, butylamine, pyridine, and 2,6-lutidine. The more preferred bases are 2,6-lutidine, triethylamine, and pyridine. The most preferred base is triethylamine.

"Biohydrolyzable ester" is an ester moiety that does not interfere with the therapeutic activity of the compound, or that is readily metabolized by a human or mammal.

"Carbocyclic aliphatic ring" is a saturated or unsaturated hydrocarbon ring. That is, carbocyclic aliphatic rings are not aromatic. Carbocyclic aliphatic rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic carbocyclic aliphatic rings contain from about 4 to about 10 carbon atoms, preferably from 4 to 7 carbon atoms, and most preferably from 5 to 6 carbon atoms in the ring. Bicyclic carbocyclic aliphatic rings contain from 8 to 12 carbon atoms, preferably from 9 to 10 carbon atoms in the ring. Carbocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred carbocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred carbocyclic aliphatic rings include cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. More preferred carbocyclic aliphatic rings include cyclohexyl, cycloheptyl, and cyclooctyl. The most preferred carbocyclic aliphatic ring is cycloheptyl.

"Corey aldehyde" is a common chemical name for hexahydro-5-hydroxy-4-formyl-2H-cyclopenta[*b*]furan-2-one, a commercially available aldehyde.

"Deprotection" refers to the removal of functional groups used to allow prior chemistries to proceed. Deprotection includes the removal of silyl ethers of alcohols or alkyl esters of carboxylic acids.

"Ether solvent" is a solvent which has two alkyl groups bonded to an oxygen, including those in which the alkyl group and oxygen are part of a ring. Preferred ether solvents include diethyl ether and tetrahydrofuran. The most preferred ether solvent is tetrahydrofuran.

"Halo" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred are chloro and fluoro, especially fluoro.

"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred haloalkyl are C_1-C_{12}; more preferred are C_1-C_6; more preferred still are C_1-C_3. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

"Halocarbon solvent" is a solvent which has one or more halogens bonded to a carbon chain. Preferred halocarbon solvents include dichloromethane, dichloroethane, carbon tetrachloride, and chloroform. More preferred halocarbon solvents include dichloromethane and chloroform. The most preferred halocarbon solvent is dichloromethane.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 1 to 18 member atoms (carbon and heteroatoms) in the chain, preferably 1 to 12, more preferably 1 to 6, more preferably still 1 to 4. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyls have one or two branches, preferably one branch. Preferred heteroalkyls are saturated. Unsaturated heteroalkyls have one or more double bonds and/or one or more triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred heteroalkyls are unsubstituted. Preferred heteroalkyl substituents include halo, hydroxy, aryl (e.g., phenyl, tolyl, alkyloxyphenyl, alkyloxycarbonylphenyl, halophenyl), heterocyclyl, heteroaryl. For example, alkyl substituted with the following substituents are heteroalkyl: alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, pentoxy), aryloxy (e.g., phenoxy, chlorophenoxy, tolyloxy, methoxyphenoxy, benzyloxy, alkyloxycarbonylphenoxy, acyloxyphenoxy), acyloxy (e.g., propionyloxy, benzoyloxy, acetoxy), carbamoyloxy, carboxy, mercapto, alkylthio, acylthio, arylthio (e.g., phenylthio, chlorophenylthio, alkylphenylthio, alkoxyphenylthio, benzylthio, alkyloxycarbonylphenylthio), amino (e.g., amino, mono- and di- C_1-C_3 alkylamino, methylphenylamino, methylbenzylamino, C_1-C_3 alkylamido, carbamamido, ureido, guanidino).

"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heterocyclic aliphatic ring" is a saturated or unsaturated ring containing carbon and from 1 to about 4 heteroatoms in the ring, wherein no two heteroatoms are adjacent in the ring and no carbon in the ring that has a heteroatom attached to it also has a hydroxyl, amino, or thiol

group attached to it. Heterocyclic aliphatic rings are not aromatic. Heterocyclic aliphatic rings are monocyclic, or are fused or bridged bicyclic ring systems. Monocyclic heterocyclic aliphatic rings contain from about 4 to about 10 ring atoms (carbon and heteroatoms), preferably from 4 to 7, and most preferably from 5 to 6 atoms in the ring. Bicyclic heterocyclic aliphatic rings contain from 8 to 12 ring atoms, preferably 9 or 10 atoms in the ring. Heterocyclic aliphatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heterocyclic aliphatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo and haloalkyl. Preferred heterocyclic aliphatic rings include piperzyl, morpholinyl, tetrahydrofuranyl, tetrahydropyranyl and piperdyl.

"Heteroaromatic ring" is an aromatic ring system containing carbon and from 1 to about 3 heteroatoms in the ring. Heteroaromatic rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaromatic rings contain from about 5 to about 10 ring atoms (carbon and heteroatoms), preferably from 5 to 7, and most preferably from 5 to 6 atoms in the ring. Bicyclic heteroaromatic rings contain from 8 to 12 ring atoms, preferably 9 or 10 atoms in the ring. Heteroaromatic rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Preferred heteroaromatic ring substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any combination thereof. More preferred substituents include halo, haloalkyl, and phenyl. Preferred heteroaromatic rings include thienyl, thiazolo, purinyl, pyrimidyl, pyridyl, and furanyl. More preferred heteroaromatic rings include thienyl, furanyl, and pyridyl. The most preferred heteroaromatic ring is thienyl.

"Hydride reducing agent" is any agent capable of delivering hydride ion in a reaction. Preferred hydride reducing agents include L-selectride, sodium borohydride, lithium aluminum hydride, and diisobutyl aluminum hydride (DIBAL). More preferred hydride reducing agents include L-selectride, sodium borohydride and DIBAL. The most preferred hydride reducing agent is DIBAL.

"Lewis acid" refers to any non-protic acid which is added to the reaction mixture to facilitate covalent bond formation. The preferred Lewis acids include magnesium perchlorate and triethylaluminum. The most preferred Lewis acid is magnesium perchlorate.

"Phenyl" is a six-membered monocyclic aromatic ring which may or may not be substituted with from about 1 to about 4 substituents. The substituents may be substituted at the *ortho*, *meta* or *para* position on the phenyl ring, or any combination thereof. Preferred phenyl substituents include: halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, phenoxy or any

combination thereof. More preferred substituents on the phenyl ring include halo and haloalkyl. The most preferred substituent is halo. The preferred substitution pattern on the phenyl ring is *ortho* or *meta*. The most preferred substitution pattern on the phenyl ring is *ortho*.

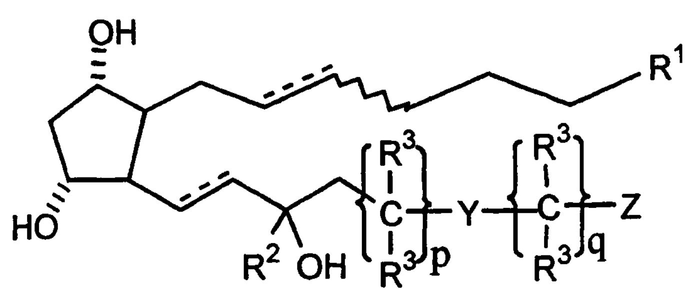
"Wadsworth-Horner-Emmons" reagent means any chemical agent suitable for adding to an aldehyde via a stabilized phosphonium salt to form an alkene bond in a single-pot process. Preferred "Wadsworth-Horner-Emmons" reagents include: 3-(2,4-dichlorophenoxy)-dimethyl-2-oxo-propyl phosphonate, 3-(2,4-difluorophenoxy)-dimethyl-2-oxo-propylphosphonate, 4-(2,6-difluorophenyl)-dimethyl-2-oxo-butylphosphonate, 3-(2,6-difluorothiophenoxy)-dimethyl-2-oxo-propylphosphonate, 4-(2-fluorophenyl)-2-oxo-butylphosphonate, 4-(3-fluoro-5-trifluoromethylphenyl)-2-oxo-butylphosphonate. This list is not meant to exclude other, similar reagents.

"Wittig-Horner" reagent is the recognized chemical name for a class of phosphonium salts which form anions that are stabilized by adjacent heteroatoms. A "Horner product" is the product formed by reaction of a compound with a Wittig-Horner reagent. See March, J. Advanced Org. Chem., 4th Ed., p. 959 (Wiley, New York, 1992)

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo Substituent Constants For Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include, for example, alkyl, alkenyl, alkoxy, hydroxy, oxo, amino, aminoalkyl, imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

II. Compounds Prepared Using the Present Process

The compounds made by the process of this invention encompass any of a variety of prostaglandin F analogs having a structure according to Formula (I):



(I)

wherein:

a) R^1 is CO_2H, C(O)NHOH, CO_2R^5, CH_2OH, $S(O)_2R^5$, $C(O)NHR^5$, $C(O)NHS(O)_2R^5$, or tetrazole (preferably CO_2H, CO_2R^5, $C(O)NHS(O)_2R^5$); wherein R^5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring (preferably alkyl);

b) R^2 is hydrogen or lower alkyl;

c) each R^3 is independently selected from the group consisting of: hydrogen, lower alkyl, alkoxy, haloalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaromatic ring (preferably hydrogen, lower alkyl, and alkoxy);

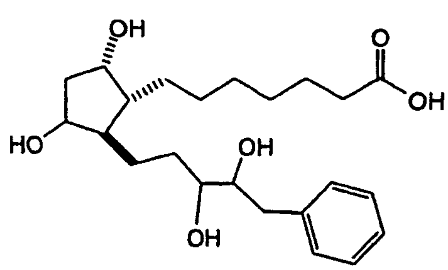
d) Y is NR^4, S, S(O), $S(O)_2$, O, or a bond (preferably NR^4, S, O, or a bond) provided that no carbon has more than one heteroatom attached to it, wherein R^4 is hydrogen, lower alkyl, or acyl (preferably hydrogen);

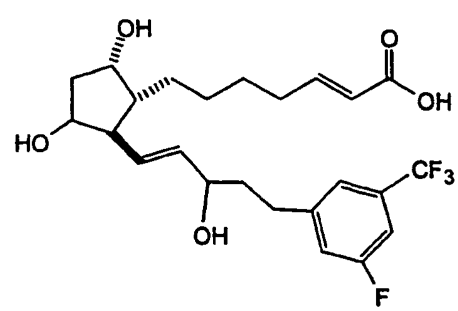
e) p is from 0 to 5 (preferably 0 or 1), q is from 0 to 5 (preferably 0 or 1), and p+q is from 0 to 5 (preferably from 0 to 2) provided that when Y is a bond p is at least 1;

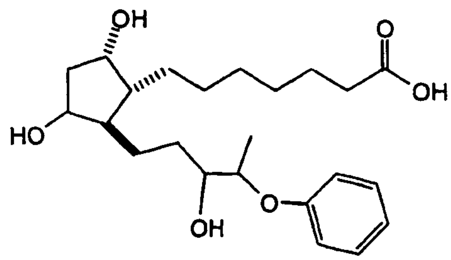
f) Z is hydrogen, methyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring provided that when Y is S, S(O), or $S(O)_2$ Z is not hydrogen (preferably carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring, more preferably the ring contains from 5 to 7 ring atoms).

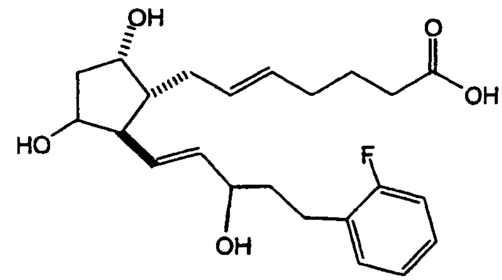
Where the compounds synthesized using the present methods are used as intermediates, groups such as sulfides, alcohols, amines and acids may be functionalized through methods known in the art.

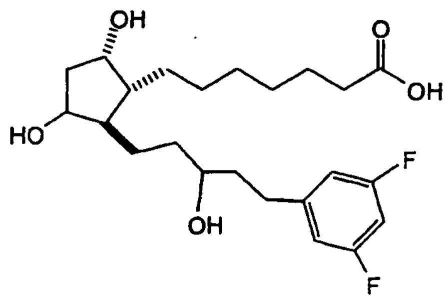
Examples of compounds which may be prepared using the process of the present invention are shown below. Theses compounds are presented for illustrative purposes only and by no means represent an exhaustive list of possibilities.

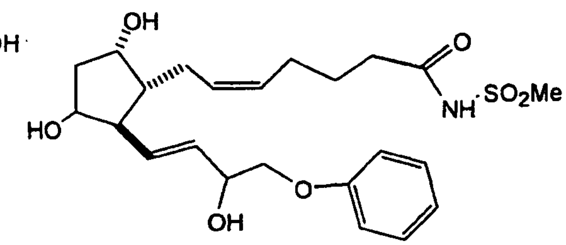










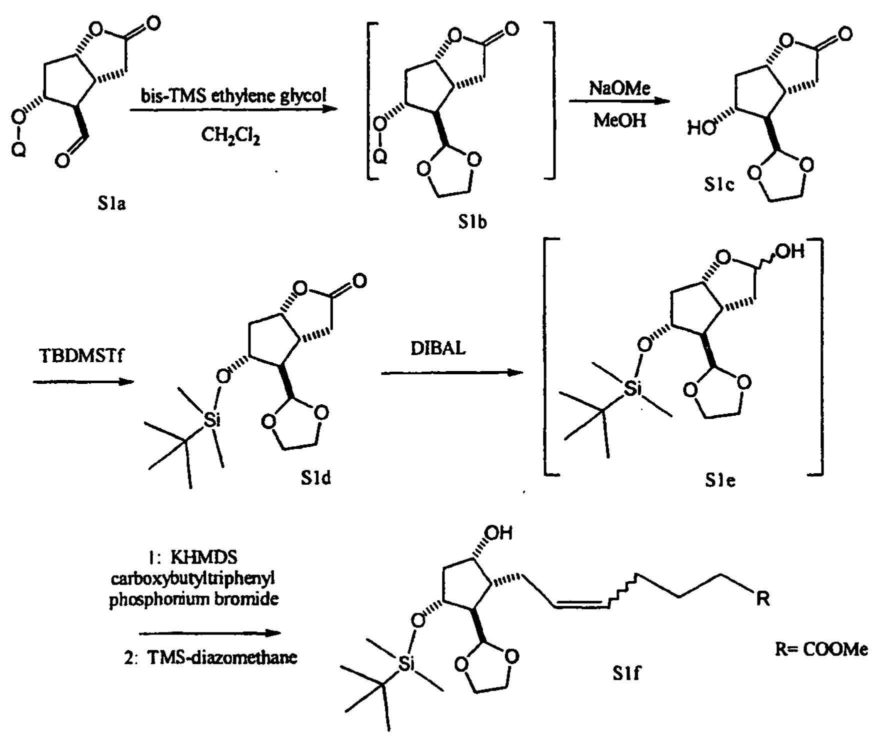


III. Methods of Manufacture and Novel Intermediates

Generally, the process of the present invention comprises the novel synthesis of the ketal intermediate described herein, followed by removal of the ketal moiety and the reaction of the intermediate under basic conditions in the presence of a Wadsworth-Horner-Emmons reagent to give, without protection of the alcohol functional groups, prostaglandin $F2_{\alpha}$ analogs, which can be further elaborated, as known in the art and herein, to 13,14-dihydro-15,16- or 17-substituted-16-tetranor or 17-trinor prostaglandin $F1_{\alpha}$ analogs. The novel ketal intermediate (**S1f** in the reaction scheme below) is synthesized in seven (7) steps, and in good yield, from the commercially available Corey Lactone.

This process is illustrated by the following general scheme:

Scheme 1



In the above general scheme:

a) R is a carboxylic acid, carboxylic acid ester comprising a saturated or unsaturated, linear or branched C_1-C_8 alkyl, aromatic hydrocarbon, hydroxamic acid, hydroxymethyl, sulfonyl amide, sulfonic acid, sulfonyl ester, or tetrazole; and

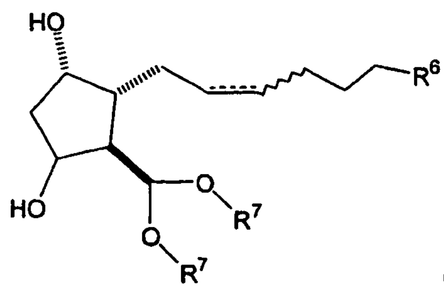
b) Q is a suitable protecting group such as a tert-butyl dimethylsilyl, trimethylsilyl, benzyl, or an alkyl C_1-C_8 ether or aromatic ether, or a benzoyl or acetyl ester.

In the above general scheme, R is more preferably a carboxylic acid or a carboxylic acid ester comprising a saturated or unsaturated, linear or branched C_1-C_8 alkyl, or aromatic hydrocarbon. R is most preferably a carboxylic acid. Preferred Q protecting groups include tert-butyl dimethylsilyl, trimethylsilyl, and benzyl ethers. The most preferred protecting group is a tert-butyl dimethylsilyl ether.

In the above general scheme, Corey aldehyde is reacted with a bis silyl-protected glycol, and a catalytic amount of acid in a solvent that will allow the ketalization to proceed. More preferred silylating agents include bis-trimethyl silyl (TMS) ethylene glycol and bis-TMS propylene glycol. The most preferred ketalization agent is bis-TMS ethylene glycol. Preferred acids include triflic acid and TMS triflate. The most preferred acid catalyst is TMS triflate. Preferred solvents include halocarbon solvents, with dichloromethane being the most preferred

solvent. The reaction is allowed to proceed at a temperature preferably between -100°C and 100°C, more preferably between -80°C and 80°C and most preferably between 0°C and 23°C.

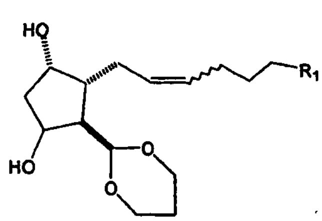
Protected ketals formed using ethylene glycol have been made previously. However, previously known chemistry generally makes these intermediates of limited utility. Applicants have discovered, surprisingly, that these intermediates can be prepared readily and are useful in making the prostaglandins of Formula (I). Applicants have further found that other diols or monohydric alcohols may be substituted for ethylene glycol to provide useful intermediates. Thus, the present invention further relates to novel intermediates having a structure according to Formula (A)

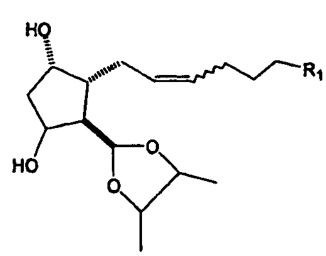


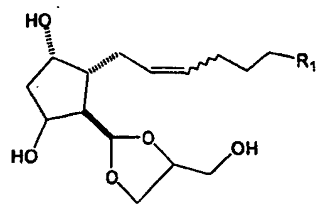
(A)

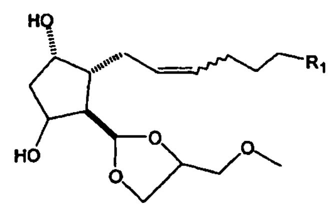
wherein R^6 is CO_2H, C(O)NHOH, CO_2R^8, CH_2OH, $S(O)_2R^8$, $C(O)NHR^8$, C(O)NH-$S(O)_2R^8$, or tetrazole, wherein R^8 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and each R^7 is (i) is lower alkyl; or (ii) the R^7 moieties together with the two oxygen atoms form a substituted 5-membered monocyclic aliphatic heterocycle, a substituted or unsubstituted 6-membered monocyclic aliphatic heterocycle, or a substituted or unsubstituted 8 to 12 member bicyclic aliphatic heterocycle; or a salt or protected form thereof.

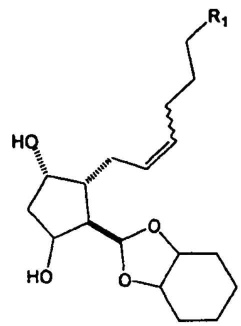
The skilled artisan will recognize what alcohol will be appropriate for forming the desired intermediate ketal. Non-limiting examples of novel Formula (A) intermediates are:

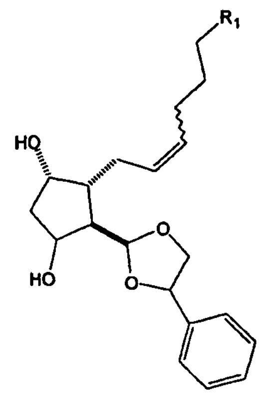


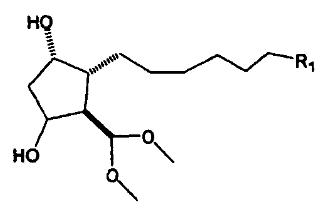












The ketal intermediate so obtained can be isolated by methods obvious to those who are skilled in the art, such methods including extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the ketal is purified after isolation by distillation under vacuum.

However, typically the ketal is reacted in the crude state with a base in a suitable solvent to remove the ester functional group from the alcohol, creating compound **S1c** in **Scheme 1**, as is typical and known in the art. Once the alcohol is formed, the reaction is neutralized, preferably with acidic ion exchange resin.

The product compound **S1c** so obtained can be isolated by methods obvious to those who are skilled in the art, such as using methods including extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the product is purified by flash chromatography on silica gel (Merck, 230-400 mesh) using 2% MeOH in CH_2Cl_2 as the eluent.

The free alcohol thus formed is reacted with a silylating agent and base in a solvent that will allow the silylation to proceed to give **S1d**, as is known in the art. The silylated compound **S1d** so obtained can be isolated by methods obvious to those who are skilled in the art, such as using methods including extraction, solvent evaporation, distillation, or crystallization

procedures. Most preferably, the silyl ether is purified after isolation by distillation under vacuum.

The product **S1d** so obtained is then treated with a special reducing agent to effect reduction of the lactone moiety to a lactol, **S1e**. The most preferred reducing agent for this process is diisobutyl aluminum hydride (DIBAL). Solvents which are preferred are benzene, heptane, xylenes, hexane and toluene. The most preferred solvent is toluene. The reaction is carried out at the beginning of the reaction preferably at between -100°C and 0°C, more preferably between -80°C and-40°C and most preferably between -80°C and -50°C. The reaction time for the initial phase of the reaction is between 5 min and 24 hours, preferably between 10 min and 4 hours, more preferably between 30 min and 3 hours. The most preferred time is between 1 hour and 2.5 hours. The reaction is then warmed to complete the process. The temperature for this part of the reaction is from about -20°C to about 20°C, more preferably from -10 to 5°C. The most preferred temperature for the second phase of the reaction is from -5 °C to 2°C. The reaction is quenched with a suitable neutralizing agent such as ammonium chloride.

The lactol **S1e** so obtained can be isolated by methods obvious to those who are skilled in the art, such as using methods including extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the lactol is purified after isolation by solvent evaporation. However, the lactol **S1e** is typically not purified but is carried on to the next step, the addition of the Wittig reagent, as is commonly described in the art (see, for example: Corey, E.J.; Weinshenker, N.M.; Schaaf, T.K.; Huber, W. "Stereo-Controlled Synthesis of Prostaglandins $F_{2\alpha}$ and E_2 (*dl*)" J. Am. Chem. Soc. 1969, 91(20), p.5675-5677]. The alkene **S1f** so obtained can be isolated by methods obvious to those who are skilled in the art, such as using methods including extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the alkene is purified after isolation by crystallization.

The alkene so created is useful as an intermediate in its own right, or it can be transformed into a useful ester. Methods for this transformation are well known in the art. Typically, the acid is transformed to the methyl ester, but it is contemplated that a variety of esters will prove useful. To create a methyl ester, typically methanol, diazomethane or TMS diazomethane is used. The most preferred reagent is TMS diazomethane. Esterification is effected by adding TMS-diazomethane dropwise to an alcoholic solution of the free acid. The reaction time is essentially instantaneous at room temperature. The reaction, however, can be run from about 5 min. to 16 hours. The most preferred time is from about 5 min to about 15

min. The reaction can also be run at a variety of temperatures, from -80 to +50 °C. The most preferred temperature is from 15°C to 25°C.

The ester so obtained can be isolated by methods obvious to those who are skilled in the art, such as using methods including extraction, solvent evaporation, distillation, or crystallization procedures. Most preferably, the alkene is purified after isolation by crystallization.

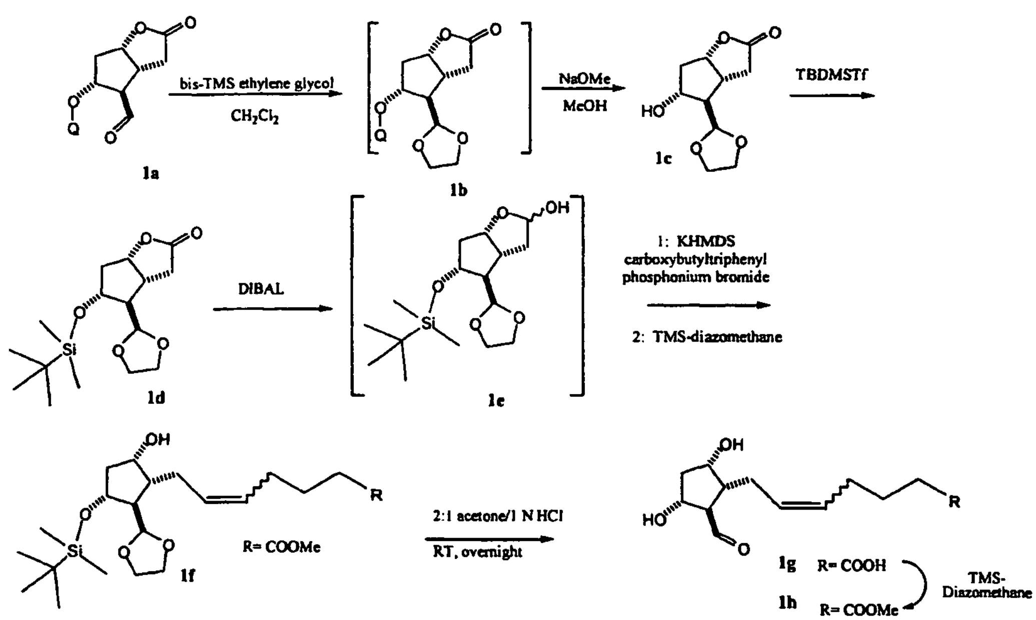
This ester is useful, as illustrated below, for the synthesis of biologically-active molecules of the prostaglandins.

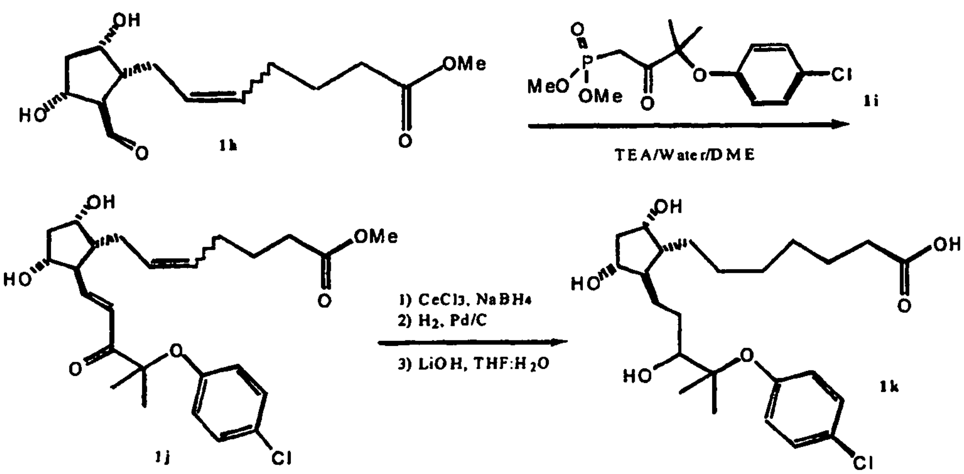
IV. Examples

The following non-limiting examples illustrate the processes of the present invention:

Example 1

Preparation of 13,14-dihydro-16,16-dimethyl,16-(4-chlorophenoxy)-16-tetranor Prostaglandin $F_{1\alpha}$





Synthesis of **1c**

In a round bottom flask equipped with a magnetic stirbar is placed 1,2-bis(trimethylsilyloxy)ethane (1.3 eq) in methylene chloride (20 mL) containing trimethylsilyl trifluoromethanesulfonate (1 mL) at -78°C. To this is added, within 20 min., a solution of **1a** (213 mmol, 1 eq) in CH_2Cl_2 (150 mL). The reaction is stirred for 1 h at -78°C and then slowly warmed to 25°C for 1 h. The reaction is quenched at 0°C with water, extracted with CH_2Cl_2 (3x100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give 67.79 g of crude **1b** (FW = 318.32 g/mole). Product formation is confirmed by MS. To a well stirred solution of crude **1b** (201 mmol, 1 eq) in methanol (786 mL) at 0°C is added a suspension of sodium methoxide (246 mmol, 1.2 eq) in MeOH (98.3 mL). The reaction is stirred at 0°C for 1 h and then warmed to 25°C for 1 h. The reaction is neutralized with acidic ion exchange resin which is washed thoroughly with MeOH (5x100 mL). The filtrate is concentrated *in vacuo* to give a syrup which is subjected to flash chromatography on silica gel eluting with 4:1 hexane : ethyl acetate and 2% MeOH in CH_2Cl_2 to give **1c** as a yellow syrup.

Synthesis of **1d**

In a round bottom flask with a magnetic stir bar, is stirred a solution of **1c** (126 mmol, 1 eq) in CH_2Cl_2 (783.6 mL). To this solution is added dropwise at -78°C 2,6-lutidine (1.9 eq) followed by TBDMSOTf (1.8 eq). The reaction stirred for 30 min. at -78°C and then warmed to 25°C overnight. The reaction is quenched with water (100 mL). The organic layer is washed with water (3x100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil which is subjected to flash chromatography on silica gel eluting with hexanes then 1% MeOH in CH_2Cl_2. The product is then washed with 1N HCl (2x100 mL), 0.1N HCl (2x100 mL), water (200 mL), and brine (2x100 mL) to give **1d**.

Synthesis of **1f**

In a round bottom flask with a magnetic stir bar, is stirred a solution of **1d** (51.9 mmol, 1 eq) in dry toluene (290 mL). To this solution, at -78°C, is slowly added DIBAL (1.24 eq). The reaction mixture is stirred for 2 h and then warmed to 0°C. Saturated NH_4Cl (50 mL) is added to the reaction mixture which is then slowly warmed to 25°C. Diluted with water (100 mL), the insoluble precipitate is removed by suction filtration and the solid is washed with EtOAc (2 x 25 mL). The liquid phase is extracted with EtOAc (3 x 50 mL) and the combined organic phase is dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow syrup. The product, 1e, should either be used immediately or stored at -70°C overnight.

To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (114 mmol, 2.2 eq) in THF (175 mL) at 0°C under N_2 is added dropwise a solution of KHMDS (456 mL of 0.5 M KHMDS in toluene, 4.4 eq). The resulting deep orange color reaction mixture is stirred for 1 h at 25°C. To the reaction mixture above at -78°C is added a solution of **1e** (1 eq) in THF (150 mL). The reaction mixture is allowed to warm to 25°C overnight. The reaction is quenched with water at 0°C and the pH is adjusted to ~3.5-4.0 with 1N HCl. The water phase is extracted with EtOAc (3x150 mL) and the combined organic phase is dried over $MgSO_4$ and is concentrated *in vacuo* to give a reddish-brown syrup containing crude acid. To a well stirred solution of crude acid in ether (800 mL) and MeOH (200 mL) at 0°C is added TMSdiazomethane until the reaction mixture keeps a light yellow color. The addition of 1 drop of glacial acetic acid, and thin layer chromatography verified the reaction had gone to completion. The reaction solution is concentrated *in vacuo* and purified via flash chromatography on silica gel eluting with 30% EtOAc in hexanes yielding **1f**.

Synthesis of **1h**

In a round bottomed flask with a magnetic stir bar is placed an amount of the ketal, **1f**. To this flask is added a sufficient amount of an admixture of 2 parts acetone to 1 part 1N HCl to bring the ketal completely into solution. This material is stirred until, by TLC, the starting material is consumed, typically overnight. The crude mixture, containing the product **1g**, is extracted with ether, and the ether extract esterified *in situ* with, preferably, TMS-diazomethane. This allows for the formation of the product **1h**, which is purified by column chromatography (30% EtOAc/hexanes) or is taken on without further purification.

Synthesis of **1i**

In a dry flask under N_2 is added 15 mL THF (anhydrous) and methyl dimethyl phosphonate (12.1 mMol) the solution is cooled to -78°C and nBuLi solution (1.1 eq, 5.5 mL of

2.5 M solution in hexanes) is added dropwise and this is stirred for one hour. The ester of 2-(4-chlorophenoxy)-2-methyl propionic acid is added dropwise in 15 mL of THF. This is stirred overnight and is allowed to warm to room temp. The crude mixture is quenched with saturated NH_4Cl then extracted with methylene chloride (2x100 mL) and purified by flash chromatography (5% MeOH in methylene chloride) to yield the yellow oil, **1i.**

Synthesis of **1j**

16,16-dimethyl-16-(4-chlorophenoxy)-15-oxo-16-tetranor $PGF_{2\alpha}$ methyl ester In a round bottom flask equipped with a magnetic stirbar is placed 3-(4-chlorophenoxy)-dimethyl-2-oxo-propylphosphonate (400 mg, 1.22 mmol, 1.65 eq) in DME (10 mL) and water (0.3 mL). To this solution is added lithium bromide (128 mg, 1.48 mmol, 2 eq), triethylamine (3.91 mmol, 5.30 eq), and methyl 7-(2-formyl-3,5-dihydroxycyclopentyl)hept-5-enoate (1.0 eq). The solution is stirred at room temperature for 24 h. Ether is added and the solution is washed once with 0.1N HCl (100 mL), and once with brine (100 mL). The organic layer is dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification is effected by silica gel column chromatography (methanol/ methylene chloride 1:49) to give the title compound, **1j**, as an oil.

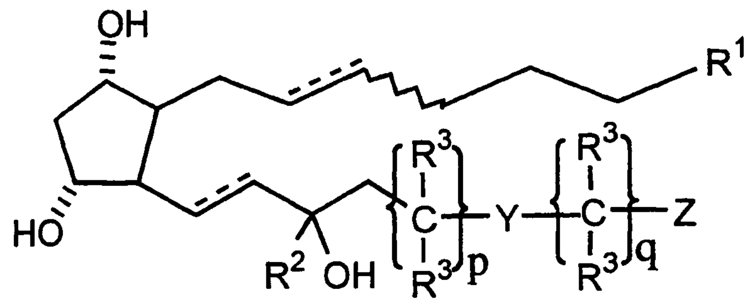
Synthesis of **1k**

13,14-dihydro-16,16-dimethyl-16-(4-chlorophenoxy)-16-tetranor $PGF_{1\alpha}$. In a flame-dried round-bottomed flask equipped with a stir bar is placed **1j** (1.0 equiv.), and cerium trichloride (1.05 equiv.) in methanol (30 mL). The solution is stirred at room temperature for 5 min. The solution is cooled to -10°C and sodium borohydride (1.02 equiv.) in methanol (0.7 mL) is added. The solution is stirred at -10°C for 3 h. The mixture is treated with water and the pH brought to ~6 with 1N HCl. The mixture is extracted twice with ethyl acetate, and the organic layers combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification is effected by silica gel column chromatography (3% methanol in dichloromethane to 5% methanol in dichloromethane) to give the 15 (*R*) alcohol and the 15 (*S*) alcohol as colorless oils. In a flame-dried round-bottomed flask equipped with a stir bar is placed one or the other of the epimeric alcohols, or a mixture thereof (1.0 equiv.) and palladium on carbon (3 mg, 10% Pd on C) in ethyl acetate (3 mL). The heterogeneous mixture is treated with hydrogen gas for 18 h. The mixture is then filtered through Celite and concentrated under reduced pressure to give the title saturated prostaglandin as the methyl ester. In a round-bottomed flask equipped with a stir bar is placed said ester (1.0 equiv.) and lithium hydroxide monohydrate (1.8 equiv.) in a 50/50 THF water solution (1.5 mL). The mixture is stirred at room temperature for 6 hours and then diluted with water and acidified to pH ~2-3 with 1N HCl. The aqueous phase is

extracted ~3 times with ethyl acetate and the organic layers combin d. The combined organic layers are dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the acid.

What is claimed is:

1. A process for making a prostaglandin F analog having a structure according to Formula (I):



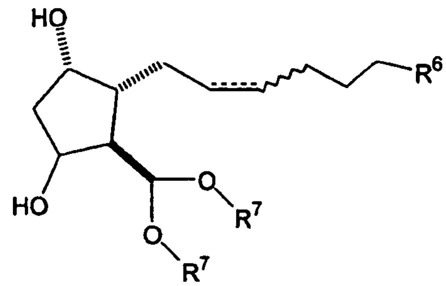
(I)

wherein:

a) R^1 is CO_2H, C(O)NHOH, CO_2R^5, CH_2OH, $S(O)_2R^5$, $C(O)NHR^5$, $C(O)NHS(O)_2R^5$, or tetrazole; characterized in that R^5 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring;
b) R^2 is hydrogen or lower alkyl;
c) each R^3 is independently selected from the group consisting of hydrogen, lower alkyl, alkoxy, haloalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, and heteroaraomatic ring;
d) Y is NR^4, S, S(O), $S(O)_2$, O, or a bond, provided that no carbon has more than one heteroatom attached to it, characterized in that R^4 is hydrogen, lower alkyl, or acyl;
e) p is from 0 to 5, q is from 0 to 5, and p+q is from 0 to 5, provided that when Y is a bond p is at least 1; and
f) Z is hydrogen, methyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring, provided that when Y is S, S(O), or $S(O)_2$, Z is not hydrogen;

the process comprising the steps of:

I) preparing an intermediat having a structure according to Formula (A):



(A)

characterized in that (A) R^6 is a carboxylic acid, a carboxylic acid ester comprising a saturated or unsaturated, linear or branched C_1-C_8 alkyl, a carbocyclic ring, a hydroxamic acid, hydroxymethyl, sulfonic acid, sulfonyl ester, sulfonyl amide, or tetrazole; and (B)(i)each R^7 is lower alkyl, or (ii) the R^7 moieties together with the two oxygen atoms form a substituted or unsubstituted 5- or 6-membered monocyclic aliphatic heterocycle or a substituted or unsubstituted 8 to 12 member bicyclic aliphatic heterocycle; or a salt or protected form thereof;

characterized in that the preparation comprises:

(a) reacting a Corey aldehyde with an activated diol or two equivalents of an activated monohydric alcohol to form an acetal derivative;

(b) deprotecting the acetal derivative of step (a) to form a hydroxy acetal;

(c) optionally reprotecting the hydroxy acetal of step (b);

(d) reducing (b) or (c) to provide a lactol derivative; and

(e) condensing the lactol derivative of step (d) with a phosphonium salt to form the intermediate ketal of Formula (A), or a salt or protected form thereof;

II) removing the ketal from the intermediate of Formula (A) formed in step (I) to form an aldehyde and coupling the aldehyde with a Wadsworth-Horner-Emmons reagent or a Wittig-Horner reagent to form a product, and

III) conducting one or more subsequent synthetic steps on the product of step (II) to form the prostaglandin F analog of Formula (I).

2. The process of Claim 1 characterized in that the two R^7 groups of Formula (A) are each lower alkyl, pr ferably methyl or ethyl, most preferably methyl.

3. The process of Claim 1 characterized in that the two R^7 groups of Formula (A) together with the two oxygen atoms form a substituted or unsubstituted (preferably

unsubstituted) 5- or 6-membered monocyclic aliphatic heterocycle, or a substituted or unsubstituted 8 to 12 member bicyclic aliphatic h terocycle.

4. The process of Claim 1 or 3 characterized in that in step I)(a) the activated diol is activated ethylene glycol or activated propylene glycol, preferably activated ethylene glycol.

5. The process of any of Claims 1-4 characterized in that the activated diol or activated monohydric alcohol comprises a silyl group, preferably trimethyl silyl.

6. The process of any of Claims 1 through 5 characterized in that the Corey aldehyde and the activated diol or activated monohydric alcohol are reacted at a temperature of from -100 to 100°C, preferably from -80 to 80°C, more preferably from 0 to 23°C to form the acetal.

7. The process of any of Claims 1-6 characterized in that prostaglandin analog has a structure according to Formula (I), wherein

a) R^1 is CO_2H, CO_2R^5, $C(O)NHS(O)_2R^5$, or tetrazole; characterized in that R^5 is alkyl;
b) R^2 is hydrogen or lower alkyl;
c) each R^3 is independently selected from the group consisting of hydrogen, lower alkyl, and alkoxy;
d) Y is NR^4, S, S(O), $S(O)_2$, O, or a bond, provided that no carbon has more than one heteroatom attached to it, characterized in that R^4 is hydrogen, lower alkyl, or acyl;
e) p is from 0 or 1, q is 0 or 1, and p+q is from 0 to 2, provided that when Y is a bond p is at least 1; and
f) Z is carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring.

8. The process of any of Claims 1- 7 charact riz d in that prostaglandin analog has a structure according to Formula (I), wherein

a) R^1 is CO_2H, CO_2R^5, $C(O)NHS(O)_2R^5$; characterized in that R^5 is lower alkyl;

b) R^2 is hydrogen or lower alkyl;

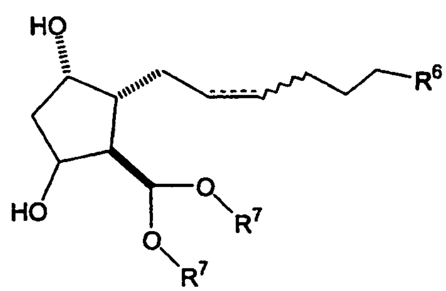
c) each R^3 is independently selected from the group consisting of hydrogen and lower alkyl;

d) Y is NR^4, S, O, or a bond, provided that no carbon has more than one heteroatom attached to it, characterized in that R^4 is hydrogen;

e) p is from 0 or 1, q is 0 or 1, and p+q is from 0 to 2, provided that when Y is a bond p is at least 1; and

f) Z is a carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; characterized in that the ring is monocylic and contains from 5 to 7 ring atoms.

9. A novel intermediate compound having a structure according to Formula (A)



(A)

characterized in that R^6 is CO_2H, C(O)NHOH, CO_2R^8, CH_2OH, $S(O)_2R^8$, $C(O)NHR^8$, C(O)NH-$S(O)_2R^8$, or tetrazole, characterized in that R^8 is alkyl, heteroalkyl, carbocyclic aliphatic ring, heterocyclic aliphatic ring, aromatic ring, or heteroaromatic ring; and each R^7 is (i) is lower alkyl; or (ii) the R^7 moieties together form a substituted 5-membered monocyclic aliphatic heterocycle, a substituted or unsubstituted 6-membered monocyclic aliphatic heterocycle, or a substituted or unsubstituted 8 to 12 member bicyclic aliphatic heterocycle; or salt or protected form thereof.

10. The novel intermediate compound of Claim 9 characterized in that R^6 is CO_2H, CO_2R^8, C(O)NH-$S(O)_2R^8$, or tetrazole, characterized in that R^8 is lower alkyl; and each R^7 is (i) is lower alkyl, preferably methyl or ethyl; or (ii) the R^7 moieties together form a substituted 5-membered monocyclic aliphatic het rocycl or a substituted or unsubstituted 6-membered monocyclic aliphatic heterocycle, preferably a substituted 5-membered or an unsubstituted 6-membered monocyclic aliphatic heterocycle.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/18595

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C405/00 //A61K31/557

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 27 57 919 A (ERBA CARLO SPA) 13 July 1978 See page 53 compound (VI)	9,10
X	DE 41 01 812 A (JENAPHARM GMBH) 30 July 1992 see abstract; figure 7	9,10
X	DE 27 43 283 A (HOECHST AG) 5 April 1979 See page 13 formula VI	9,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 1998	09/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	JOHNSON, FRANCIS ET AL: "Prostaglandins. 2. Synthesis of prostaglandin F2.alpha. in optically active form from chiral precursors" J. AM. CHEM. SOC. (1982), 104(8), 2190-8 CODEN: JACSAT;ISSN: 0002-7863,1982, XP002085508 See scheme IV, page 2194 -----	1-18

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Information on patent family members

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